REMARKS/ARGUMENTS

In the specification, the paragraph beginning at page 1, line 1, has been amended to update the status of the claim of priority. The specification has been further amended to correctly indicate registered Trademarks by capitalizing the word.

Regarding the Notice of Draftsperson's Patent Drawing Review, applicants concurrently submit a new corrected drawing of Figure 7 to the Official Draftsperson. A copy of the Letter to the Official Draftsperson is submitted herewith.

Claims 8-12 are pending in this application.

Priority

2. Applicants have amended the first line of the specification to indicate that U.S. application no. 09/210,168 is "now U.S. Patent No. 6,355,424."

Information Disclosure Statement

3. Applicants acknowledge that DE 44 45 769 C1 was not reviewed by the Examiner because the reference is in the German language. Applicants provide herewith a corresponding English language patent, U.S. Patent No. 5,786,337 which claims priority to DE 44 45 769.3. Applicants also acknowledge that EP0502994B1 was not reviewed by the Examiner and submit herewith EP0502994B1. Reconsideration of these foreign patents is respectfully requested. Applicants request that DE 44 45 769 C1 and EP502 994 on FORM PTO-1449 be initialed and returned.

Specification

5. Applicants have amended the specification by capitalizing and accompanying the generic terminology for the trademarks as suggested by the Examiner. The specification has also been amended for clarification or to correct typographical errors. No new matter has been added by these amendments.

Rejections Under 35 U.S.C. §112

7. Claims 8-12 have been rejected under 35 U.S.C. §112, first paragraph, because the Examiner contends that the specification and art lack guidance and would require undue experimentation to use the claimed invention "with respect to diagnosis and/or monitoring of cancer in a patient by determination of the HPV gene transcript ratios of the claims, including HPV16 gene transcript ratios." The Examiner also contends that the specification does not provide evidence that the HPV gene transcript ratios set forth in the claims are associated with transformation, cancer, disease stage, etc., in a patient." Further, the Examiner contends that "the prior art is silent with respect to a correlation or correspondence between HPV gene transcript ratios measured in the particular cell culture models employed by applicants and ratios measured in, e.g., different types of tissues samples taken from patients." Applicants respectfully disagree with the Examiner's grounds of rejection.

The Examiner contends that because HPV16 mRNA ratios other than (E6 + E7)/L1 were not detectable (ND) in HaCaT cells, and the ratios varied in the two other cell types, *i.e.*, W12 and SiHa cells, as reported in Table 2, the instant invention is allegedly unpredictable for one skilled in the art to practice the claimed invention. Applicants respectfully disagree with the Examiner's contention.

Applicants respectfully direct the Examiner's attention to pages 9-12 which generally describe how ratios of HPV genes are related to HPV-associated disease stages. Table 1 on page 9 describes the expected level of HPV genes. From reading Table 1 and Table 2, one skilled in the art understands that in low grade CIN (CIN1) tissues, HPV genes, such as E6, E7, E2, E4, L1, and L2, may not be detectable, *i.e.*, a ratio value less than 2. Applicants assert that the ratios of other HPV gene combinations for W12 and SiHa cells in Table 2 other than (E6 + E7)/L1 and the specification together enable one skilled in the art to diagnose HPV-associated diseases. The Examiner's attention is respectfully directed to page 10, second paragraph of the instant specification which provides guidelines as to HPV gene ratios that correspond to HPV-based disease states.

The Examples further describe how to practice the claimed invention in detail using HPV 16 as an example. In particular, Example 1 describes how to detect and analyze nucleic acids, while Example 2 illustrates how to measure HPV mRNA, including but not limited to,

E6/E7. Examples 3 and 4 describe quantitation of HPV16 mRNA in cells of varying stages of infection and malignancy. Specific working examples of all possible combinations need not be shown if one skilled in the art understands how to make and use the invention as described. As the Examiner is well aware, the specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art would be able to practice it without an undue amount of experimentation according to MPEP§2164.02, *In re* Borkowski, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970).

The Examiner contends that there is no evidence that the HPV gene transcript ratios are associated with transformation, cancer, disease stage in a patient. However, applicants respectfully disagree. Enclosed herewith is declaratory evidence establishing the validity of various types of cultured cells used as similarly provided in 09/210,168, in addition to data for HPV 18 and HPV 31.

Applicants assert that the cell line models described in the specification, i.e., HaCaT, W12, and SiHa, correlate to stages of HPV-induced disease in patients; there is a strong correlation between HPV infection and cancer; and the claimed diagnostic assays are useful in diagnosis of these HPV-induced diseases in patients as is discussed in the attached declaration. Applicants further assert that the claims are fully enabled as the disclosure teaches how to make and use the assays for screening purposes in patients.

The claims describe patients infected or suspected of infection with human papillomavirus. A patient infected or suspected of infection with human papillomavirus is not any type of patient as the Examiner contends. Thus, with respect to "a patient infected with HPV," applicants assert the claims are fully enabled.

Applicants' invention describes and enables diagnosis of HPV-induced neoplasia, disease, and cancer of any HPV type. In fact, a determination of the type of HPV itself may be used in the diagnosis. For example, the specification describes that "Specific human papillomavirus types, including HPV 6 and 11, frequently cause benign mucosal lesions, whereas other types, HPV 16, 18, and a host of other strains, are predominantly found in high-grade lesions and cancer." (Page 1, lines 22-25). In the attached declaration, Dr. Lorincz points to zur Hausen (1996, Biochimica et Biophysica Acta, 1288, F55-F78) which describes HPV types 1-70 and provides a description of their involvement in the etiology of

human diseases. For example, Table 1 of zur Hausen reports that at least 17 different HPV types are preferentially found in melanoma, carcinoma and cancer and that another 18 HPV types are preferentially found in neoplasias. Thus, the claims are fully enabled with respect to diagnosing a patient infected or suspected of being infected with HPV.

Claims 8-12 are enabled by the specification and what was known and understood in the art at the time of filing. The Examiner contends that the prior art is silent with respect to a correlation between HPV gene transcript ratios and disease. However, the Examiner admits that Stoler, et al. (*Human Pathology* 23:2, 1992) demonstrate that HPV E6 and E7 genes have elevated expression. The Examiner contends that the types and quantities of HPV transcripts vary depending on cancer type, HPV type, and cell or tissue location. Applicants assert that although the types of HPV are associated with different diseases, the instant specification enables one skilled in the art to assess the disease stage and/or risk from measuring HPV gene transcripts, and more particularly, the HPV gene transcript ratios.

Finally, applicants present a 37 C.F.R. §1.132 declaration and Curriculum Vitae of inventor Attila Lorincz, Ph.D. Dr. Lorincz provides evidence in the declaration that HPV infection has been confirmed to be the cause of virtually all cases of cervical cancer and that HPV infection is found in a high percentage of non-melanoma skin cancers, in cancers of the oral cavity, the larynx, and the esophagus, and is the cause of a variety of intraepithelial neoplasias and many types of hyperkeratoses. Dr. Lorincz's declaration also provides evidence establishing a correlation between cell line models, such as W12, HaCaT, and SiHa, and cancer in a human patient. Further, Dr. Lorincz's declaration provides evidence that such cell lines are universally recognized by researchers as model systems of human epithelium in a patient at various states progressing to cancer. Examples for HPV 18 and HPV 31 mRNA ratios further demonstrate that the mRNA ratios, i.e., E6, E7, L1, etc., of other HPV types may be used to diagnose and prognose a subject having an HPV-associated disease or condition.

Therefore, in light of the amendment and arguments presented above, applicants assert that the scope of the present claims is fully enabled. Reconsideration and withdrawal of the 37 C.F.R. §112, first paragraph rejection is respectfully requested.

Double Patenting Rejection

9. Claims 8-12 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, respectively, of U.S. Patent No. 6,355,424B1. Applicants respectfully disagree with this rejection as being premature. However, should claims be allowed and issue into a U.S. patent, applicants will consider the advisability of filing a terminal disclaimer at that time.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for the timely consideration of this amendment under 37 C.F.R. §§ 1.16 and 1.17, or credit any overpayment to Deposit Account No. 13-4500, Order No. 2629-4005US4.

Respectfully submitted,

MORGAN & FINNEGAN, L.L.P.

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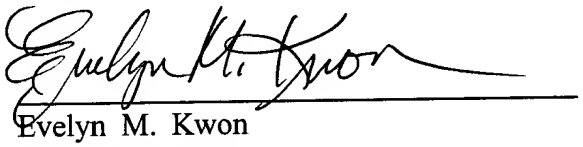
By: 
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